IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BOARD OF PATENT APPEALS AND INTERFERENCES

Applicant: Gary Griffiths

Title: FLUORINATION OF PROTEINS AND PEPTIDES FOR F-18 POSITRON EMISSION TOMOGRAPHY

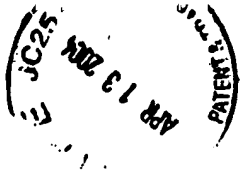
Appl. No.: 10/071,247

Filing Date: 02/11/2002

Examiner: Huynh, P.

Art Unit: 1644

REPLY BRIEF



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Attorney Docket No. 018733/1093

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APPELLANT'S REPLY BRIEF UNDER 37 CFR §1.193

Commissioner for Patents
PO Box 1450
Alexandria, Virginia 22313-1450

Sir:

This Reply Brief responds to the Examiner's Answer mailed February 13, 2004 in the captioned appeal. It is believed that no fees are due with the submission of this brief. In the event any fees are required for the filing of this paper, please charge such fees to Deposit Account No. 08-1641.

I. ARGUMENT

A. The Claimed Invention is Fully Enabled and the Examiner's Answer is Based on a Misconception of the Invention.

Appellant respectfully submits that the arguments set forth in the Examiner's Answer reflect a misconception regarding the claimed invention. The claimed invention involves, *inter alia*, a method of detecting a tissue using a bispecific antibody or

antibody fragment where one arm of the antibody binds the tissue and the second arm binds a labeled peptide or hapten conjugate. The Examiner does not contest Appellant's demonstration that methods of generating antibodies against essentially any antigen are well known in the art, nor that methods of making bispecific antibodies that recognize two distinct antigens also are well known. Rather, the gravamen of the Examiner's case apparently is:

> The specification does not teach how to make and use all bispecific or humanized monoclonal antibody or Fab fragment thereof where one arm is specific for *all* target tissue of the patient and the other arm is specific for all undisclosed F-18-labeled peptide, all low molecular weight hapten conjugated to *all* F-18-labeled peptide mentioned above for a method for PET imaging.

Answer at 4-5 (emphasis in original). The Examiner appears under some misapprehension about the nature of the labeled peptide or hapten, and relies heavily on a citation to an 11-page section of the Kuby textbook on Immunology, cited for the proposition that:

> immunizing a peptide comprising a contiguous amino acid sequence of 8 amino acid residues or a protein derived from a full-length polypeptide *may* result in antibody specificity that differs from antibody specificity directed against the native full-length polypeptide.

Examiner's Answer at 10 (emphasis added). Later in the Answer the Examiner abandons this conditional statement and recasts the purported teaching in Kuby as an iron-clad rule:

> Kuby et al reference establishes that antibody specificity generated from a fragment differs from antibody specificity directed against the native full-length polypeptide.

Answer at 8 (emphasis added). Appellant demonstrates below that, not only is the Examiner's reliance on Kuby scientifically inaccurate but that, even if it were an accurate reflection of the textbook, it is insufficient to sustain the Examiner's burden of coming forward with adequate evidence to demonstrate that the application is not enabled. In addition, the general tenor of the Examiner's remarks apparently reflects a misconception of the invention.

As an initial matter, appellant notes that the Examiner fails to specify what part, if any, of the 11 cited pages of the Kuby reference supports the proposition that anti-peptide antibodies would not be expected to bind to the same peptide within a native protein. Appellant has reviewed the reference and respectfully submits that nothing in the cited reference stands for the cited proposition. If this is incorrect, appellant respectfully requests that the Examiner provide a specific citation of a passage in Kuby that supports the proposition.

At best, Kuby provides discussion of the nature of epitopes in peptides and globular proteins and states that B-cell epitopes tend to be situated in flexible regions of proteins. Kuby at 96, left column. However, this statement contradicts the Examiner's assertions, because it is well known that antibodies that bind to peptide sequences corresponding to mobile areas within proteins also bind to the proteins themselves. See, for example, Tainer *et al.*, *Nature* 312:127 (1984)(abstract appended hereto) which states (emphasis added):

> To study the nature of antigenic recognition, antibodies have been prepared against a set of peptide sequences representing both highly mobile and well-ordered regions of myohaemerythrin, based on X-ray crystallographic temperature factors. Anti-peptide antibodies against highly mobile regions react strongly with the native protein; anti-peptide antibodies from well-ordered regions do not. Mobility is a major factor in the recognition of the native protein by anti-peptide antibodies; this may be of general significance in protein-protein interactions

To recap: Kuby states that B-cell epitopes tend to be in flexible regions, and Tainer states that anti-peptide antibodies against flexible (mobile) regions react strongly with native protein. Accordingly, one skilled in the art would expect that anti-peptide antibodies would react strongly with native protein. Even a brief perusal of a catalogue of commercially available antibodies would support this conclusion, since hundreds or even thousands of anti-peptide antibodies are sold commercially as tools for studying native proteins. However, this conclusion is the polar opposite of that drawn by the Examiner from Kuby. Appellant respectfully requests that the Examiner provide a specific citation from Kuby in support of the instant rejection, or withdraw the rejection.

In any event, even if were true, as the Examiner first asserts, that anti-peptide antibodies *may* not recognize native protein, this is insufficient, for at least two reasons, to sustain the rejection here. First, the mere fact that the Examiner may imagine a circumstance where an anti-peptide antibody within the scope of the appealed claims may not recognize a native protein does not meet the Examiner's burden of overcoming the presumption that a specification is enabling. It is not a function of the claims to specifically exclude either possible inoperative substances or ineffective reactant proportions. See In re Dinh-Nguyen, 181 USPQ 46, 48 (CCPA 1974). Thus, possible inoperativeness is not a proper criterion for rejecting the claims.

Second, and perhaps more significantly, the Examiner's assertion appears to be irrelevant to the claimed invention. One skilled in the art seeking to practice the claimed methods would use a bispecific antibody that reacts with (i) a desired target and (ii) a labeled peptide or hapten. The fact that the bispecific antibody may or may not react with the labeled peptide sequence if, for some unexplained reason, the peptide was contained within a large protein, seems irrelevant. All that is required for enablement is that the skilled worker be able to prepare a bispecific antibody with the desired specificity for a target and for a desired labeled peptide. The Examiner presents no evidence that this is not within the ability of the skilled artisan.

At page 10 of the Answer the Examiner demonstrates a misconception of the invention:

> Until the time when such bispecific antibody that binds to *all* F-I 8-labeled peptide and targeted tissue is made or identified, then one skilled in the art can use the bispecific antibodies or binding fragment thereof for imaging for the claimed method.

This appears to indicate that the Examiner considers the claimed invention to require some kind of omni-specific antibody that will bind to *any* F18 labeled peptide and to *any* target. This clearly is not what the claims require. All that is required is that the bispecific antibody bind to *a* target and to *a* labeled peptide or hapten. The skilled artisan will select or make a particular bispecific antibody that reacts with a particular target and a particular peptide or hapten, and the antibody will change as the binding

partners change. It is uncontroverted that the skilled artisan can prepare bispecific antibodies that recognize a target and a peptide or hapten. Accordingly, the claimed invention is fully enabled and the rejection should be withdrawn.

B. The specification also provides a written description of the invention that clearly apprises those of skill in the relevant art that appellant had possession of the claimed invention at the time of filing.

The Examiner rejects the claims for lack of written description, stating:

> Further, Appellant disclose only three F-18-labeled peptides, there is a lack of a written description of *all* additional F-18-labeled peptide, low molecular weight hapten conjugated F-i 8-labeled peptide, let alone all bispecific antibody or fragment thereof that binds to all tissue and all F-18-labeled peptide for a method for detecting a tissue by positron emission tomography as broadly as claimed. Until the binding specificity of the bispecific antibody and the F- 18 labeled peptide in the claimed method are adequately described, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus.

Answer at 21 (emphasis in original). Apparently, therefore, the Examiner believes that the instant specification must describe *all* possible bispecific antibodies, peptides and haptens to meet the criteria of § 112, first paragraph. This is an impossible standard to meet and is not required by the law. Appellant's claimed methods are generally applicable and can be used with any target amenable to detection by a bispecific antibody and with any labeled peptide or hapten amendable to capture by a bispecific antibody. To require appellant to specify each and every antibody that might fall within the ambit of his claims requires that appellant unnecessarily limit those claims. This practically invites misappropriation of the invention by third parties, who need merely apply appellant's teachings to a combination of target and peptide that is not specified in detail in the specification. The law is not intended to promote such an unjust result.

For each claim drawn to a genus, as in claim 9, the written description requirement may be satisfied through sufficient description of a representative number of species representative of the entire genus. The Examiner has failed to describe why

the examples provided in the instant specification are not representative of the claimed genus. A mere statement that the number of species is insufficient cannot, without more, meet the Examiner's burden here. As stated in appellant's Appeal Brief, what constitutes a "representative number" is an inverse function of the skill and knowledge in the art. Satisfactory disclosure of a "representative number" depends on whether one skilled in the art would recognize that the appellant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed. It is uncontroverted that the level of skill in the relevant art is high and it behooves the Examiner to explain with particularity why the species described in the specification are not representative of the claimed genus. The Examiner has not provided such an explanation and therefore the rejection should be withdrawn.

II. CONCLUSION

For these reasons, the Board is respectfully requested to reverse the examiner and remand this application for issuance.

Respectfully submitted,

April 13, 2004
Date

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1: Nature. 1984 Nov 8-14;312(5990):127-34. Related Articles, Links

The reactivity of anti-peptide antibodies is a function of the atomic mobility of sites in a protein.

Tainer JA, Getzoff ED, Alexander H, Houghten RA, Olson AJ, Lerner RA, Hendrickson WA.

To study the nature of antigenic recognition, antibodies have been prepared against a set of peptide sequences representing both highly mobile and well-ordered regions of myohaemerythrin, based on X-ray crystallographic temperature factors. Anti-peptide antibodies against highly mobile regions react strongly with the native protein; anti-peptide antibodies from well-ordered regions do not. Mobility is a major factor in the recognition of the native protein by anti-peptide antibodies; this may be of general significance in protein-protein interactions.

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